Journal of Zhejiang University-SCIENCE B (Biomedicine & Biotechnology) *2025 26(2):145-157*
www.jzus.zju.edu.cn; www.springer.com/journal/11585
E-mail: jzus_b@zju.edu.cn

Research Article

https://doi.org/10.1631/jzus.B2300730

Efficacy of adjunctive systemic or local antibiotic therapy in peri-implantitis: a systematic review and meta-analysis of randomized controlled clinical trials

Yifan LU, Siqi BAO, Hongke LUO, Qianming CHEN✉, Misi SI✉

Stomatology Hospital, School of Stomatology, Zhejiang University School of Medicine, Zhejiang Provincial Clinical Research Center for Oral Diseases, Key Laboratory of Oral Biomedical Research of Zhejiang Province, Cancer Center of Zhejiang University, Engineering Research Center of Oral Biomaterials and Devices of Zhejiang Province, Hangzhou 310000, China

Abstract: This systematic review and meta-analysis considered the results of randomized controlled clinical trials (RCTs) to evaluate the efficacy of systemic or local antibiotic therapy in peri-implantitis. Two independent authors screened publications from three electronic databases to include RCTs meeting all the inclusion and exclusion criteria. A meta-analysis was performed to evaluate the weighted mean differences in survival rate (SR) and changes in pocket probing depth (PPD), bone level (BL), and clinical attachment level (CAL). The study cohorts were defined as antibiotic and control groups with subgroups for analysis. Seven studies including 309 patients (390 implants) were considered. Within the limitations of this review, patients in the antibiotic groups exhibited significant improvements in PPD. Subgroup analysis indicated that the administration of systemic antibiotics or the use of antibiotics in non-surgical treatments did not result in a significant alteration in BL. It was established that the addition of antibiotics can ameliorate PPD and SR in the treatment of peri-implantitis, whether through surgical or non-surgical approaches, and also shows moderate performance regarding BL and CAL. Considering the lack of application of new technologies in the control group and the hardship of assessing the potential risks of antibiotics, careful clinical judgment is still necessary.

Key words: Peri-implantitis; Dental implant; Oral medicine; Microbiology; Disease management; Meta-analysis

1 Introduction

Peri-implantitis is characterized by the inflammation and progressive loss of supporting bone tissue surrounding a functioning dental implant, leading to irreversible damage (Zitzmann et al., 2001). In recent studies, the prevalence of peri-implantitis has been found to be 19.0% and 11.2% among patients and implants, respectively (Zhang et al., 2018). This condition is associated with progressive bone loss, bone resorption, impaired osseointegration, increased pocket formation, and the presence of purulent discharge (Smeets et al., 2014; Lee et al., 2017). In addition, a notable positive association has been established between the occurrence of peri-implantitis and the length of implant function (Derks and Tomasi, 2015). Currently, peri-implantitis treatment methods can reach a high implant survival rate (SR), with around three-quarters of implants treated for peri-implantitis still present after five years; however, disease recurrence, bone loss progression, and implant loss still occur (Heitz-Mayfield et al., 2018), demonstrating that there is still room for improvement.

According to a recent evaluation, the risk factors associated with peri-implantitis development include poor plaque control, smoking, infrequent periodontal treatment, a history of periodontitis, excess cement, insufficient keratinized mucosa, diabetes, and other systemic diseases (Darby, 2022). Similar to that in periodontitis (Zhao et al., 2023), all of the aforementioned conditions impair the capacity to remove dental plaque, which is still thought to be the primary etiological

---

✉ Qianming CHEN, qmchen@zju.edu.cn
Misi SI, misi_si@zju.edu.cn
Yifan LU, https://orcid.org/0009-0009-4158-9345
Qianming CHEN, https://orcid.org/0000-0002-5371-4432
Misi SI, https://orcid.org/0000-0001-5352-2046

Received Oct. 18, 2023; Revision accepted Apr. 1, 2024;
Crosschecked Oct. 29, 2024; Published online Nov. 7, 2024

agent of peri-implantitis (Berglundh et al., 2018). As a result, therapeutical techniques aiming at plaque management are critical for treating peri-implantitis.

A range of therapies have been applied, including non-surgical and surgical treatments, with the former being successful for peri-mucositis but inconclusive for peri-implantitis (Claffey et al., 2008; Khoshkam et al., 2013; Chan et al., 2014). According to research, it is difficult to reduce bacterial loads to the threshold level for disease transmission using simply mechanical measures (Renvert et al., 2007; Figuero et al., 2014; Heitz-Mayfield and Mombelli, 2014). As a result, monotherapy may not be effective for disease control, prompting the consideration of surgical therapy and adjuvant devices.

The utility of antibiotics as adjunctive therapy has been demonstrated in controlling intra-oral biofilm, managing clinical symptoms, and promoting radiographic bone regeneration (Keestra et al., 2015; Cha et al., 2019). According to the study by Graziani et al. (2017), the use of systemic antibiotics could be crucial in managing conditions primarily attributed to bacterial plaque. Extensive evidence supports its efficacy in both non-surgical and surgical interventions for periodontitis under specific circumstances (Rovai et al., 2016; Santos et al., 2016). Moreover, it is posited that adjunctive antibiotic therapy should be considered for the treatment of peri-implantitis owing to the etiological commonalities, and numerous clinical studies were conducted to assess the effectiveness of this approach (Mombelli and Lang, 1992; Smeets et al., 2014; Carcuac et al., 2016).

In contrast, antibiotics can lead to adverse effects, like resistance and dysbiosis, among other undesirable outcomes (Singh et al., 2014). Reviews on the efficacy of antibiotics have indicated that additional randomized controlled clinical trials (RCTs) are required to validate their usage (Klinge et al., 2002; Grusovin et al., 2022). In specific instances, the administration of adjunctive pharmacotherapy did not confer additional enhancement in clinical or microbiological outcomes compared to mechanical debridement or surgical intervention as monotherapy (Santos et al., 2016; Carcuac et al., 2017). Therefore, researchers are exploring alternative treatments such as laser therapy, antimicrobial photodynamic therapy, and antibacterial medicines (Li et al., 2022; Yong et al., 2023). However, whether these treatment modalities can replace antibiotics still requires further investigations in academic research. Currently, some scholars have conducted meta-analyses on the efficacy of adjunctive antibiotic therapy in treating peri-implantitis; however, most of them have been limited to interventions in surgical or non-surgical treatment settings (Keestra et al., 2015; Rovai et al., 2016; Grusovin et al., 2022; Baus-Domínguez et al., 2023; Teughels et al., 2023). In a review encompassing both surgical and non-surgical treatments (Wang et al., 2022), subgroup analyses were performed only on local or systemic antibiotic administrations, with the conflation of peri-implantitis and mucositis in the analysis. Furthermore, the outcome measures in current meta-analyses are far from comprehensive.

This review investigated the outcomes of implants treated for peri-implantitis by surgical or non-surgical methods, comparing the results with or without supplementary antibiotics through a meta-analysis. The objective was to assess whether antibiotics demonstrate superior efficacy in treatment for peri-implantitis. A systematic umbrella review concerning this topic has been conducted (Boccia et al., 2023); however, a detailed analysis pertinent to the subject is lacking. Our study exclusively included RCTs to acquire higher-quality outcomes. Pocket probing depth (PPD), bone level (BL), and clinical attachment level (CAL) changes and implant SR were evaluated.

2 Methods

2.1 Focused question: Population, Intervention, Comparison, and Outcome (PICO)

The PICO approach was adopted to ask the focused question: “Can adjunctive antibiotics demonstrate superior efficacy, compared to other adjuvant approaches, in the treatment of peri-implantitis?”

The PICOS elements included: Population (P), based on available evidence, patients affected by peri-implantitis; Intervention (I), systematic or local antibiotic treatment as an adjunct; Comparison (C), treatment with other alternative options or no adjunctive treatment; Outcome (O), the evaluation of outcomes methodically conducted by measuring alterations in PPD, BL, and CAL, in addition to SR; Study (S), RCTs.

2.2 Eligibility criteria

The inclusion criteria for articles were established as follows: (1) at least three months of follow-up for adults in good general health; (2) identification of peri-implantitis with precision through research; (3) antibiotics evaluated in peri-implantitis research against other adjuvant treatments; (4) changes in clinical parameters compared at the implant level to determine effectiveness, including PPD decreases, CAL gains, and BL gains; (5) the study written in English language; and (6) the study designed as randomized controlled clinical trial.

The following exclusion criteria were applied to evaluate pre-selected studies: (1) peri-implantitis lacking a clear clinical definition; (2) medication type or dosage not described in sufficient detail; (3) duplicate studies; (4) systematic reviews, in vitro studies, cross-over studies, commentaries, case reports, unpublished articles, and letters to the editor; (5) data given only at the patient level but not the implant level.

2.3 Information source

All relevant articles were collected from PubMed, Embase, and Cochrane Central Register of Controlled Trials (CENTRAL) by the researchers. The search included English publications up until July 1, 2023. Additionally, to ensure comprehensive coverage, the reference lists of chosen articles were independently examined to identify potential studies that could have been missed during the initial search.

Two authors (namely Yifan LU and Siqi BAO) independently conducted the data extraction. Discrepancies were resolved either until consensus was reached via discussion or by seeking input from a third author.

Initially, the eligibility criteria were applied to exclude articles by evaluating their titles or abstracts. Afterwards, a more refined selection was achieved by screening the full texts.

The essential features of each study were outlined, encompassing details such as the primary author, publication year, research methodology, enrollment size of patients or implants, groups, interventions, diagnostic standards, outcome assessments, and durations of follow-up. In cases where information was missing, efforts were undertaken through email communication to reach out to the corresponding author with the intention of acquiring comprehensive data. In the absence of a response, an identical email was forwarded to the co-authors. Should there be no reply, the study was excluded from the analysis.

2.4 Search strategy

The searching strategy was as follows: (“drug delivery” OR “drug implants” OR “drug compounding” OR “drug release” OR “local drug treatment” OR “medication” OR “drug treatment” OR “antibacterial agents” OR “local drug administration” OR “anti-microbial” OR “bactericides” OR “anti-infective agents” OR “antibiotics” OR “systemic antibiotics” OR “antibiotic prophylaxis”) AND (“peri-implantitis” OR “periimplantitis” OR “peri-implant disease*” OR “peri-implant infection” OR “peri-implantitides” OR “peri-implant bone loss” OR “periimplant mucositis” OR “periimplant” OR “peri-implant mucositis” OR “dental implant inflammation” OR “peri-implant”) AND “randomized controlled trial.”

2.5 Effect measures and synthesis methods

The mean±standard deviation (SD) effect measures were used to record all outcomes. In the case where there was a minimum of two studies featuring similar interventions and observation time that could be compared, Review Manager (RevMan, Version 5.3 for Mac) was utilized to perform a meta-analysis, merging the data for each outcome measurement. To assess heterogeneity among the studies, I^2 statistics were employed: I^2 values falling within the range of 25%–50% suggested low heterogeneity; values within 50%–75% indicated medium heterogeneity; values exceeding 75% denoted high heterogeneity (Higgins et al., 2003). Significant heterogeneity was deemed present when the I^2 statistics surpassed 50%. In instances of non-significant heterogeneity ($I^2 \leqslant 50\%$), fixed-effects models were employed. Conversely, random-effects models were used in cases of significant heterogeneity ($I^2 > 50\%$) (Higgins et al., 2003). The criterion for statistical significance was set at $P<0.05$. The findings of the analysis were presented using forest plots, displaying the weighted mean difference (WMD) along with a 95% confidence interval (CI). All outcomes were calculated at the implant level.

The studies were categorized into two subgroups for analysis: (1) patients who received surgical or non-surgical treatment, and (2) patients who used systemic or local antibiotics.

2.6 Reporting bias assessment

The screened human clinical articles were evaluated for bias risk using the Cochrane Collaboration tool (Higgins et al., 2011). This assessment considers various factors such as detection bias, selection bias, performance bias, and biases of other sources. Each item was classified as having a low, high, or unclear risk of bias. An overall estimation of bias risk was determined for each study based on a cumulative score. The study was regarded as having a low risk of bias if all the items were evaluated as low. In contrast, when any item was deemed to have an unclear or high risk of bias, that study was evaluated as one with an unclear or high risk of bias.

3 Results

3.1 Study selection

The flowchart of the literature search and screening process is presented in Fig. 1. Seven studies were included in the systematic review, featuring a total of 309 patients (390 implants).

3.2 Study characteristics

The included studies were summarized in Tables S1 and S2, providing an overview of the research. Across these studies, the average ages of patients varied between 58.31 and 66.30 years, and the follow-up periods ranged from 3 to 12 months. All studies provided information on smoking habits, with four of them specifically focusing on nonsmokers (Cha et al., 2019; Shibli et al., 2019; Emanuel et al., 2020) or light smokers (Park et al., 2021). Four studies recorded the history of periodontal disease (Carcuac et al., 2016; Cha et al., 2019; Blanco et al., 2022; Polymeri et al., 2022), and the groups were comparable at the beginning of the research. Four studies described the type of implant used: one study mentioned only the implant brand (Polymeri et al., 2022), one study only specified the implant surface (Park et al., 2021), and the remaining two studies included multiple types of implants, providing details on both implant brand and surface (Carcuac et al., 2016; Cha et al., 2019).

Detailed treatment information in the included studies was listed in Table S3. The protocols for debridement and ultrasonic instruments implemented in the non-surgical treatment included Teflon curettes (Shibli et al., 2019), polyether ether ketone (PEEK), fiber tip with carbon fiber reinforced plastic hand instruments (Polymeri et al., 2022), and ultrasonic steel scaling inserts (Park et al., 2021; Blanco et al., 2022). Despite variations among studies, the maintenance protocols were outlined in all of them. Two studies used 0.12% (volume fraction) chlorhexidine, with one instructing patients to rinse it off after treatment (Polymeri et al., 2022), and the other using it

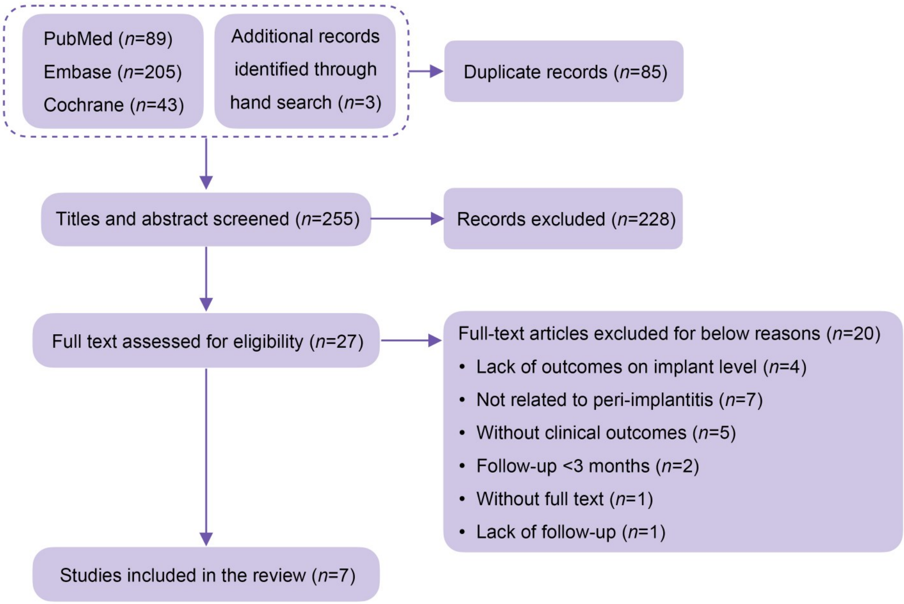


Fig. 1 Flowchart of the process of literature search and selection.

before, during, and after the debridement (Blanco et al., 2022). In studies using surgical treatment, subgingival scaling/debridement with the open-flap technique was applied. The use of local anesthesia was reported in all three studies (Carcuac et al., 2016; Cha et al., 2019; Emanuel et al., 2020). Adjunctive antibiotics were administered either locally (Cha et al., 2019; Emanuel et al., 2020; Park et al., 2021) or systemically (Carcuac et al., 2017; Shibli et al., 2019; Blanco et al., 2022; Polymeri et al., 2022).

3.3 Risk of bias across studies

An overview of the assessment of bias risk was presented in Fig. 2. Not all studies provided detailed descriptions of blinding and randomized allocation methods. None of the studies were classified as having a low risk of bias, five studies were categorized as having an unclear risk of bias (Carcuac et al., 2016; Cha et al., 2019; Shibli et al., 2019; Park et al., 2021; Polymeri et al., 2022), and the remaining studies were deemed to have a high risk of bias (Emanuel et al., 2020; Blanco et al., 2022).

3.4 Meta-analysis

3.4.1 Synthesis of results for changes in pocket probing depths

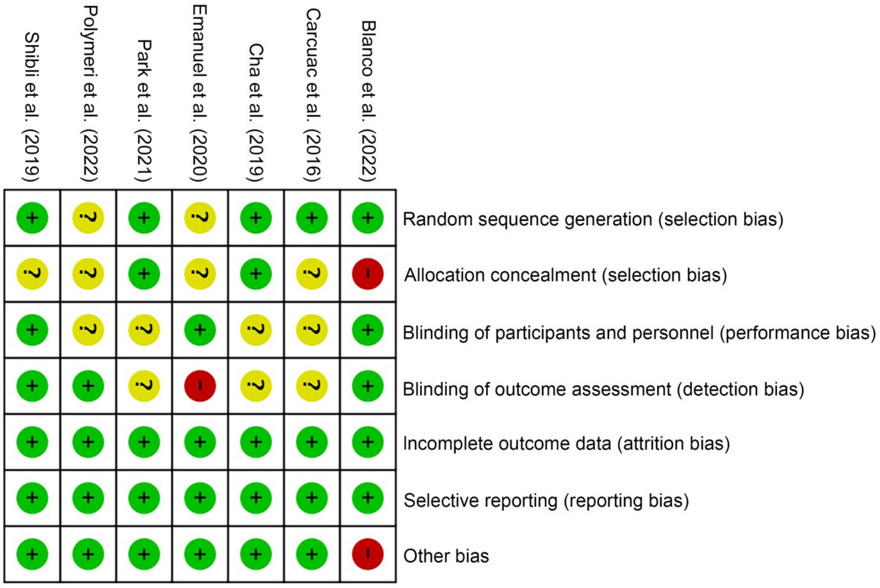
In general, the utilization of adjunctive antibiotics demonstrated marked improvement in PPD reduction compared to controls (WMD=1.10, 95% CI 0.78 to 1.43, $P<0.00001$; Fig. 3). Moreover, the beneficial effects of both surgical and non-surgical treatments, in combination with local or systemic antibiotics, were also evident in the subgroup analysis. Fortunately, heterogeneity in the subgroups was considered relatively low (I^2 in both systemic and local antibiotic subgroups equaled 0%, and I^2 in surgical subgroup equaled 37%), except for slightly higher heterogeneity in the non-surgical subgroup (I^2=58%).

3.4.2 Synthesis of results for survival rates

Six studies provided comparisons of SRs between adjunctive antibiotics and control groups. Consistency in defining treatment success was observed in six studies. The antibiotic group demonstrated enhanced treatment efficacy compared to the control group (weighted pooled odds ratio=2.37; 95% CI 1.53 to 3.65, P=0.0001; Fig. 4). Similar results were found in subgroups (Fig. 4), and the heterogeneity test results were satisfactory ($I^2 \leqslant 20\%$).

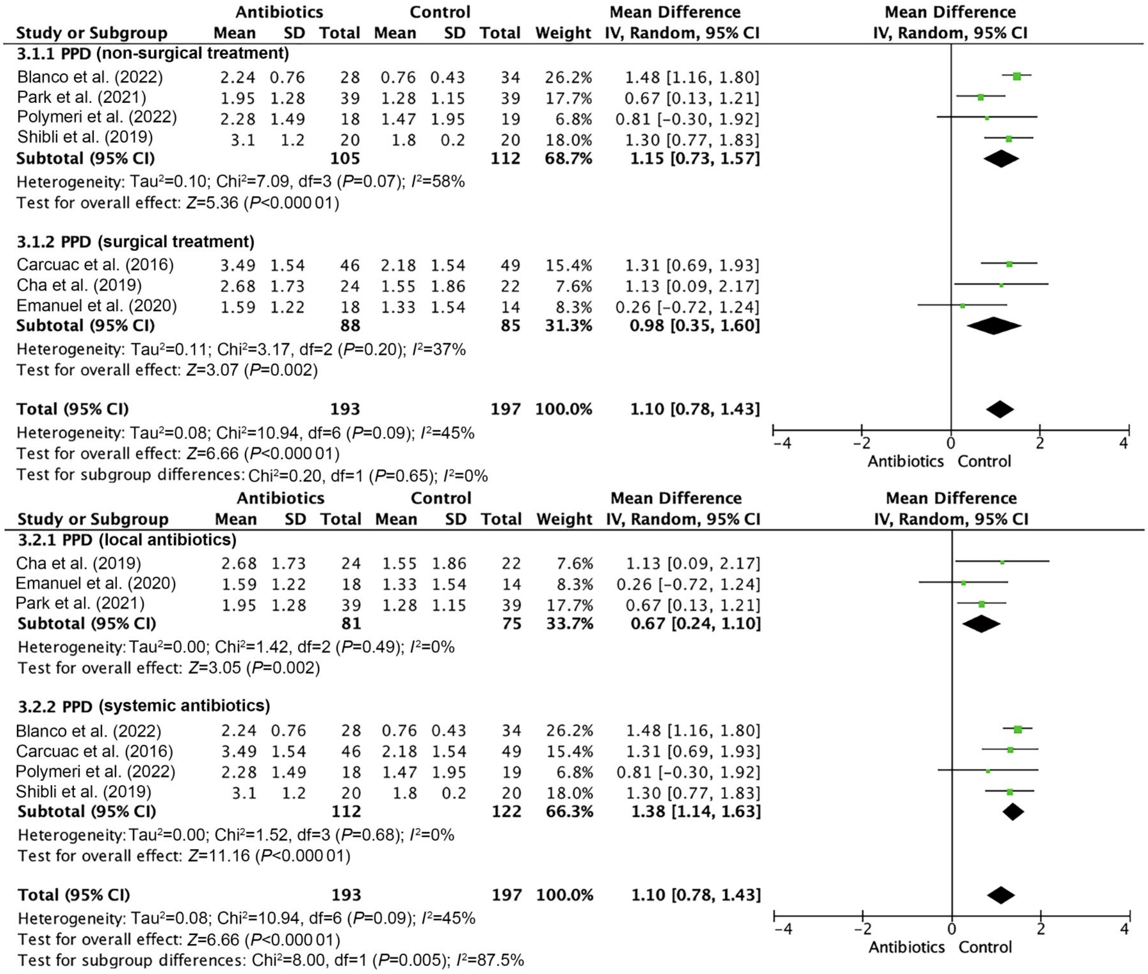
3.4.3 Synthesis of results for changes in clinical attachment levels

Only three studies assessed the changes in CAL over a 12-month period. Significantly reduced attachment loss was observed in the groups receiving antibiotics as compared to the control group, according to



Shibli et al. (2019)	Polymeri et al. (2022)	Park et al. (2021)	Emanuel et al. (2020)	Cha et al. (2019)	Carcuac et al. (2016)	Blanco et al. (2022)	
+	?	+	?	+	+	+	Random sequence generation (selection bias)
?	?	+	?	+	?	-	Allocation concealment (selection bias)
+	?	?	+	?	?	+	Blinding of participants and personnel (performance bias)
+	+	?	-	?	?	+	Blinding of outcome assessment (detection bias)
+	+	+	+	+	+	+	Incomplete outcome data (attrition bias)
+	+	+	+	+	+	+	Selective reporting (reporting bias)
+	+	+	+	+	+	-	Other bias

Fig. 2 Summary of bias risk. Each round marker represents the result of each study's assessment of different bias-risk items, with color of green, yellow, and red presenting low, unclear, and high risk of bias, respectively.



Study or Subgroup	Antibiotics Mean	Antibiotics SD	Antibiotics Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
3.1.1 PPD (non-surgical treatment)								
Blanco et al. (2022)	2.24	0.76	28	0.76	0.43	34	26.2%	1.48 [1.16, 1.80]
Park et al. (2021)	1.95	1.28	39	1.28	1.15	39	17.7%	0.67 [0.13, 1.21]
Polymeri et al. (2022)	2.28	1.49	18	1.47	1.95	19	6.8%	0.81 [−0.30, 1.92]
Shibli et al. (2019)	3.1	1.2	20	1.8	0.2	20	18.0%	1.30 [0.77, 1.83]
Subtotal (95% CI)			**105**			**112**	**68.7%**	**1.15 [0.73, 1.57]**
Heterogeneity: Tau²=0.10; Chi²=7.09, df=3 (*P*=0.07); *I*²=58%								
Test for overall effect: *Z*=5.36 (*P*<0.000 01)								
3.1.2 PPD (surgical treatment)								
Carcuac et al. (2016)	3.49	1.54	46	2.18	1.54	49	15.4%	1.31 [0.69, 1.93]
Cha et al. (2019)	2.68	1.73	24	1.55	1.86	22	7.6%	1.13 [0.09, 2.17]
Emanuel et al. (2020)	1.59	1.22	18	1.33	1.54	14	8.3%	0.26 [−0.72, 1.24]
Subtotal (95% CI)			**88**			**85**	**31.3%**	**0.98 [0.35, 1.60]**
Heterogeneity: Tau²=0.11; Chi²=3.17, df=2 (*P*=0.20); *I*²=37%								
Test for overall effect: *Z*=3.07 (*P*=0.002)								
Total (95% CI)			**193**			**197**	**100.0%**	**1.10 [0.78, 1.43]**
Heterogeneity: Tau²=0.08; Chi²=10.94, df=6 (*P*=0.09); *I*²=45%								
Test for overall effect: *Z*=6.66 (*P*<0.000 01)								
Test for subgroup differences: Chi²=0.20, df=1 (*P*=0.65); *I*²=0%								

Study or Subgroup	Antibiotics Mean	Antibiotics SD	Antibiotics Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
3.2.1 PPD (local antibiotics)								
Cha et al. (2019)	2.68	1.73	24	1.55	1.86	22	7.6%	1.13 [0.09, 2.17]
Emanuel et al. (2020)	1.59	1.22	18	1.33	1.54	14	8.3%	0.26 [−0.72, 1.24]
Park et al. (2021)	1.95	1.28	39	1.28	1.15	39	17.7%	0.67 [0.13, 1.21]
Subtotal (95% CI)			**81**			**75**	**33.7%**	**0.67 [0.24, 1.10]**
Heterogeneity: Tau²=0.00; Chi²=1.42, df=2 (*P*=0.49); *I*²=0%								
Test for overall effect: *Z*=3.05 (*P*=0.002)								
3.2.2 PPD (systemic antibiotics)								
Blanco et al. (2022)	2.24	0.76	28	0.76	0.43	34	26.2%	1.48 [1.16, 1.80]
Carcuac et al. (2016)	3.49	1.54	46	2.18	1.54	49	15.4%	1.31 [0.69, 1.93]
Polymeri et al. (2022)	2.28	1.49	18	1.47	1.95	19	6.8%	0.81 [−0.30, 1.92]
Shibli et al. (2019)	3.1	1.2	20	1.8	0.2	20	18.0%	1.30 [0.77, 1.83]
Subtotal (95% CI)			**112**			**122**	**66.3%**	**1.38 [1.14, 1.63]**
Heterogeneity: Tau²=0.00; Chi²=1.52, df=3 (*P*=0.68); *I*²=0%								
Test for overall effect: *Z*=11.16 (*P*<0.000 01)								
Total (95% CI)			**193**			**197**	**100.0%**	**1.10 [0.78, 1.43]**
Heterogeneity: Tau²=0.08; Chi²=10.94, df=6 (*P*=0.09); *I*²=45%								
Test for overall effect: *Z*=6.66 (*P*<0.000 01)								
Test for subgroup differences: Chi²=8.00, df=1 (*P*=0.005); *I*²=87.5%								

Fig. 3 Forest plot of pocket probing depth (PPD) and meta-analyses for the comparison of PPD changes. SD: standard deviation; CI: confidence interval; IV: inverse variance; df: degree of freedom.

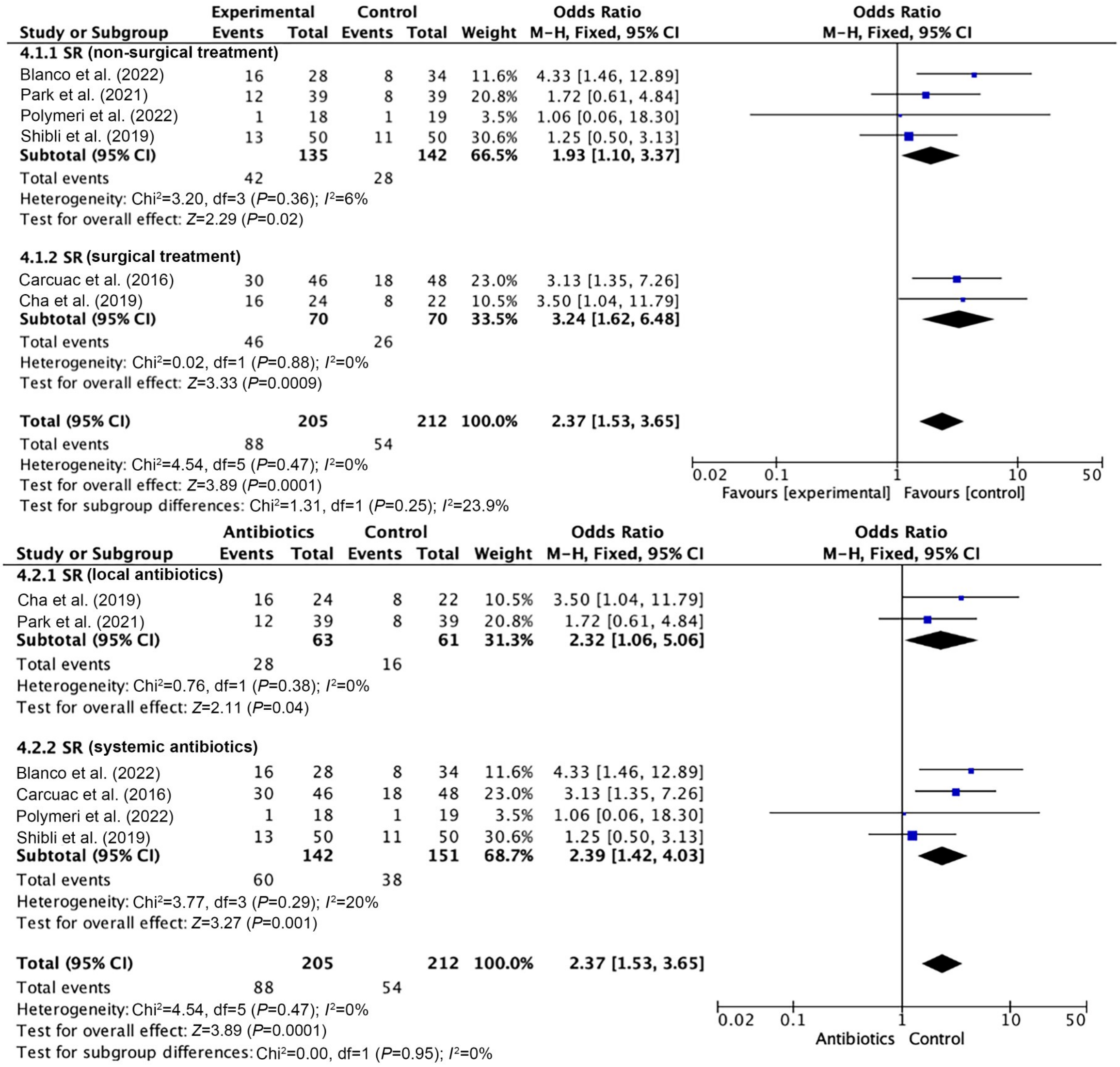
the meta-analysis (WMD=1.28, 95% CI 1.00 to 1.55, $P<0.000\,01$; Fig. 5). The result was similar when considering the condition using non-surgical treatment plus adjunctive systemic antibiotics (WMD=1.34, 95% CI 1.05 to 1.62, $P<0.000\,01$; Fig. 5) with low heterogeneity ($I^2=0\%$).

3.4.4 Synthesis of results for changes in bone levels

Changes in the BL for five researches differed significantly between the two groups (WMD=0.80, 95% CI 0.25 to 1.34, $P=0.004$; Fig. 6). In addition, a great amount of heterogeneity was found ($\text{Chi}^2=49.47$, $I^2=92\%$; $P<0.000\,01$). When focusing on the results of subgroup analysis, those taking surgical method or local antibiotics showed remarkable higher BLs in antibiotic groups (Fig. 6), but the heterogeneity results were both high ($I^2=81\%$ and $I^2=75\%$, respectively).

4 Discussion

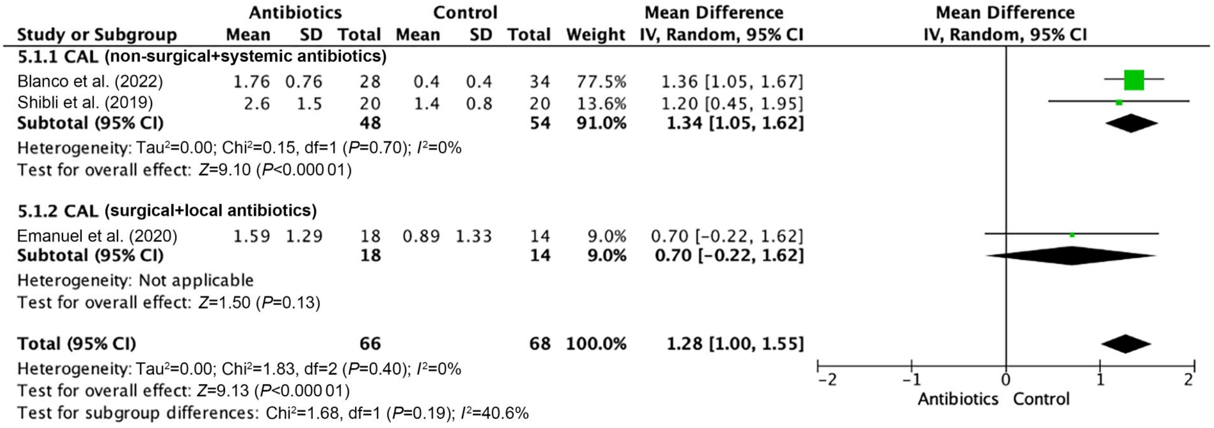
Overall, notable clinical benefits were observed when treating peri-implantitis with the inclusion of supplementary antibiotics. These benefits included a significant reduction in PPD, improved BL, enhanced CAL, and overall treatment success. When subgroup analysis was conducted, it was observed that the benefits of antibiotics were particularly pronounced in terms of PPD reduction and treatment success across all treatment methods. In addition, antibiotics in conjunction with surgical therapy or local antibiotics resulted in reduced bone loss compared to control



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
4.1.1 SR (non-surgical treatment)						
Blanco et al. (2022)	16	28	8	34	11.6%	4.33 [1.46, 12.89]
Park et al. (2021)	12	39	8	39	20.8%	1.72 [0.61, 4.84]
Polymeri et al. (2022)	1	18	1	19	3.5%	1.06 [0.06, 18.30]
Shibli et al. (2019)	13	50	11	50	30.6%	1.25 [0.50, 3.13]
Subtotal (95% CI)		**135**		**142**	**66.5%**	**1.93 [1.10, 3.37]**
Total events	42		28			
Heterogeneity: Chi^2=3.20, df=3 (P=0.36); I^2=6%						
Test for overall effect: Z=2.29 (P=0.02)						
4.1.2 SR (surgical treatment)						
Carcuac et al. (2016)	30	46	18	48	23.0%	3.13 [1.35, 7.26]
Cha et al. (2019)	16	24	8	22	10.5%	3.50 [1.04, 11.79]
Subtotal (95% CI)		**70**		**70**	**33.5%**	**3.24 [1.62, 6.48]**
Total events	46		26			
Heterogeneity: Chi^2=0.02, df=1 (P=0.88); I^2=0%						
Test for overall effect: Z=3.33 (P=0.0009)						
Total (95% CI)		**205**		**212**	**100.0%**	**2.37 [1.53, 3.65]**
Total events	88		54			
Heterogeneity: Chi^2=4.54, df=5 (P=0.47); I^2=0%						
Test for overall effect: Z=3.89 (P=0.0001)						
Test for subgroup differences: Chi^2=1.31, df=1 (P=0.25); I^2=23.9%						

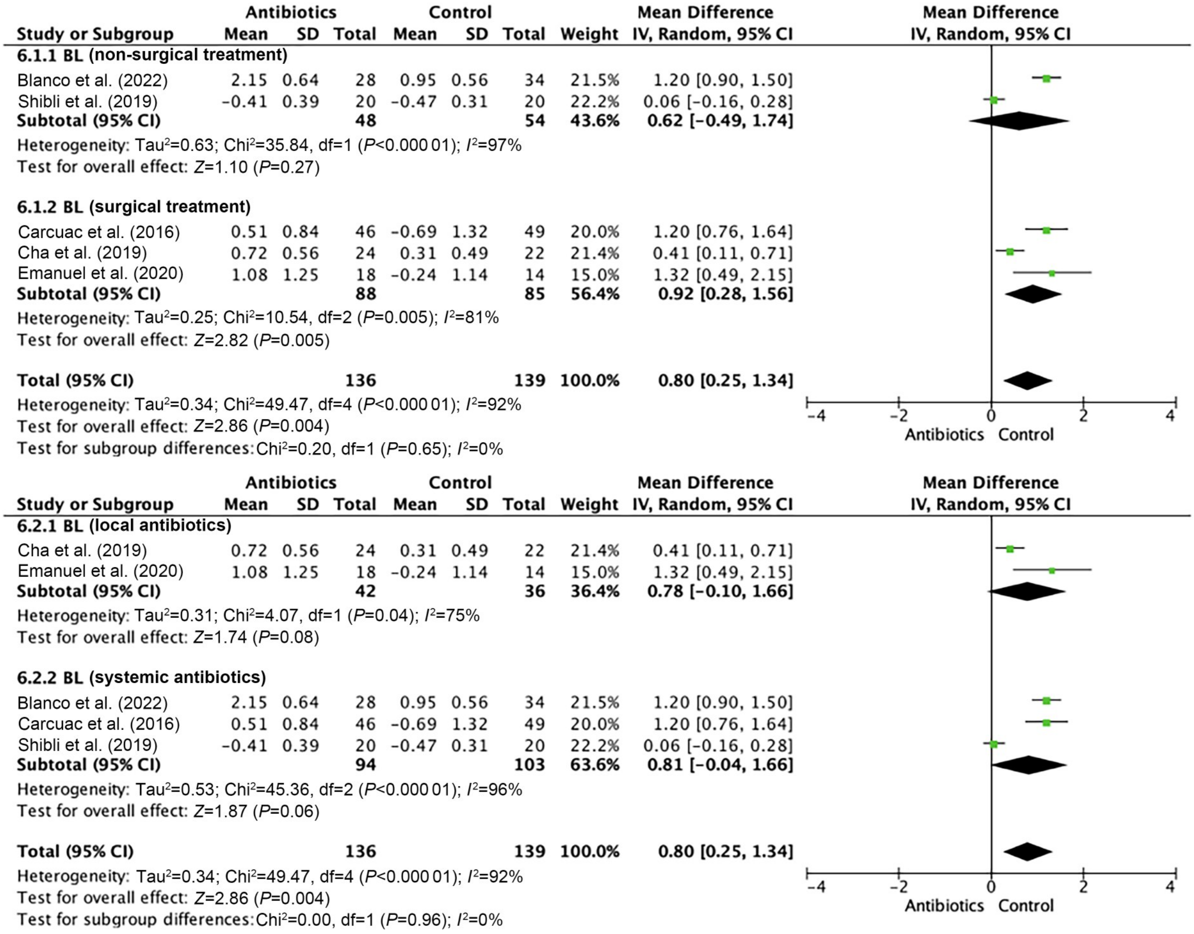
Study or Subgroup	Antibiotics Events	Antibiotics Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
4.2.1 SR (local antibiotics)						
Cha et al. (2019)	16	24	8	22	10.5%	3.50 [1.04, 11.79]
Park et al. (2021)	12	39	8	39	20.8%	1.72 [0.61, 4.84]
Subtotal (95% CI)		**63**		**61**	**31.3%**	**2.32 [1.06, 5.06]**
Total events	28		16			
Heterogeneity: Chi^2=0.76, df=1 (P=0.38); I^2=0%						
Test for overall effect: Z=2.11 (P=0.04)						
4.2.2 SR (systemic antibiotics)						
Blanco et al. (2022)	16	28	8	34	11.6%	4.33 [1.46, 12.89]
Carcuac et al. (2016)	30	46	18	48	23.0%	3.13 [1.35, 7.26]
Polymeri et al. (2022)	1	18	1	19	3.5%	1.06 [0.06, 18.30]
Shibli et al. (2019)	13	50	11	50	30.6%	1.25 [0.50, 3.13]
Subtotal (95% CI)		**142**		**151**	**68.7%**	**2.39 [1.42, 4.03]**
Total events	60		38			
Heterogeneity: Chi^2=3.77, df=3 (P=0.29); I^2=20%						
Test for overall effect: Z=3.27 (P=0.001)						
Total (95% CI)		**205**		**212**	**100.0%**	**2.37 [1.53, 3.65]**
Total events	88		54			
Heterogeneity: Chi^2=4.54, df=5 (P=0.47); I^2=0%						
Test for overall effect: Z=3.89 (P=0.0001)						
Test for subgroup differences: Chi^2=0.00, df=1 (P=0.95); I^2=0%						

Fig. 4 Forest plot of survival rate (SR) and meta-analyses for the comparison of SR. SD: standard deviation; CI: confidence interval; M-H: Mantel-Haenszel; df: degree of freedom.



Study or Subgroup	Antibiotics Mean	Antibiotics SD	Antibiotics Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
5.1.1 CAL (non-surgical+systemic antibiotics)								
Blanco et al. (2022)	1.76	0.76	28	0.4	0.4	34	77.5%	1.36 [1.05, 1.67]
Shibli et al. (2019)	2.6	1.5	20	1.4	0.8	20	13.6%	1.20 [0.45, 1.95]
Subtotal (95% CI)			**48**			**54**	**91.0%**	**1.34 [1.05, 1.62]**
Heterogeneity: Tau^2=0.00; Chi^2=0.15, df=1 (P=0.70); I^2=0%								
Test for overall effect: Z=9.10 (P<0.000 01)								
5.1.2 CAL (surgical+local antibiotics)								
Emanuel et al. (2020)	1.59	1.29	18	0.89	1.33	14	9.0%	0.70 [−0.22, 1.62]
Subtotal (95% CI)			**18**			**14**	**9.0%**	**0.70 [−0.22, 1.62]**
Heterogeneity: Not applicable								
Test for overall effect: Z=1.50 (P=0.13)								
Total (95% CI)			**66**			**68**	**100.0%**	**1.28 [1.00, 1.55]**
Heterogeneity: Tau^2=0.00; Chi^2=1.83, df=2 (P=0.40); I^2=0%								
Test for overall effect: Z=9.13 (P<0.000 01)								
Test for subgroup differences: Chi^2=1.68, df=1 (P=0.19); I^2=40.6%								

Fig. 5 Forest plot of clinical attachment level (CAL) and meta-analyses for the comparison of CAL. SD: standard deviation; CI: confidence interval; IV: inverse variance; df: degree of freedom.



Study or Subgroup	Antibiotics Mean	Antibiotics SD	Antibiotics Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
6.1.1 BL (non-surgical treatment)								
Blanco et al. (2022)	2.15	0.64	28	0.95	0.56	34	21.5%	1.20 [0.90, 1.50]
Shibli et al. (2019)	−0.41	0.39	20	−0.47	0.31	20	22.2%	0.06 [−0.16, 0.28]
Subtotal (95% CI)			**48**			**54**	**43.6%**	**0.62 [−0.49, 1.74]**
Heterogeneity: Tau^2=0.63; Chi^2=35.84, df=1 (P<0.000 01); I^2=97%								
Test for overall effect: Z=1.10 (P=0.27)								
6.1.2 BL (surgical treatment)								
Carcuac et al. (2016)	0.51	0.84	46	−0.69	1.32	49	20.0%	1.20 [0.76, 1.64]
Cha et al. (2019)	0.72	0.56	24	0.31	0.49	22	21.4%	0.41 [0.11, 0.71]
Emanuel et al. (2020)	1.08	1.25	18	−0.24	1.14	14	15.0%	1.32 [0.49, 2.15]
Subtotal (95% CI)			**88**			**85**	**56.4%**	**0.92 [0.28, 1.56]**
Heterogeneity: Tau^2=0.25; Chi^2=10.54, df=2 (P=0.005); I^2=81%								
Test for overall effect: Z=2.82 (P=0.005)								
Total (95% CI)			**136**			**139**	**100.0%**	**0.80 [0.25, 1.34]**
Heterogeneity: Tau^2=0.34; Chi^2=49.47, df=4 (P<0.000 01); I^2=92%								
Test for overall effect: Z=2.86 (P=0.004)								
Test for subgroup differences: Chi^2=0.20, df=1 (P=0.65); I^2=0%								

Study or Subgroup	Antibiotics Mean	Antibiotics SD	Antibiotics Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
6.2.1 BL (local antibiotics)								
Cha et al. (2019)	0.72	0.56	24	0.31	0.49	22	21.4%	0.41 [0.11, 0.71]
Emanuel et al. (2020)	1.08	1.25	18	−0.24	1.14	14	15.0%	1.32 [0.49, 2.15]
Subtotal (95% CI)			**42**			**36**	**36.4%**	**0.78 [−0.10, 1.66]**
Heterogeneity: Tau^2=0.31; Chi^2=4.07, df=1 (P=0.04); I^2=75%								
Test for overall effect: Z=1.74 (P=0.08)								
6.2.2 BL (systemic antibiotics)								
Blanco et al. (2022)	2.15	0.64	28	0.95	0.56	34	21.5%	1.20 [0.90, 1.50]
Carcuac et al. (2016)	0.51	0.84	46	−0.69	1.32	49	20.0%	1.20 [0.76, 1.64]
Shibli et al. (2019)	−0.41	0.39	20	−0.47	0.31	20	22.2%	0.06 [−0.16, 0.28]
Subtotal (95% CI)			**94**			**103**	**63.6%**	**0.81 [−0.04, 1.66]**
Heterogeneity: Tau^2=0.53; Chi^2=45.36, df=2 (P<0.000 01); I^2=96%								
Test for overall effect: Z=1.87 (P=0.06)								
Total (95% CI)			**136**			**139**	**100.0%**	**0.80 [0.25, 1.34]**
Heterogeneity: Tau^2=0.34; Chi^2=49.47, df=4 (P<0.000 01); I^2=92%								
Test for overall effect: Z=2.86 (P=0.004)								
Test for subgroup differences: Chi^2=0.00, df=1 (P=0.96); I^2=0%								

Fig. 6 Forest plot of bone level (BL) and meta-analyses for the comparison of BL. SD: standard deviation; CI: confidence interval; IV: inverse variance; df: degree of freedom.

groups. It is noteworthy that, for the subgroup receiving non-surgical treatment combined with systemic antibiotics, a significant improvement was reported at the CAL, which was not observed in other subgroups.

4.1 Local and systemic antibiotics

The substantial variability identified in the studies reporting BLs (I^2=92%; Fig. 6) can be explained by the varied measurements employed in the different researches and whether they were performed by more than one individual. For example, Shibli et al. (2019) measured the distance between the levels of the abutment and the top of the alveolar ridge with intraoral radiographs, whereas Emanuel et al. (2020) evaluated this parameter with standardized periapical radiographs relating to the reference point of implant; additionally, In the study by Carcuac et al. (2016), two investigators separately measured the mean values, which was not mentioned in other studies.

In the studies concerned by this review, the use of antibiotics as systemic adjuvant could significantly ameliorate peri-implant inflammation in the short term, which was also proved in other meta-analyses (Grusovin et al., 2022; Feres et al., 2023). However, other reviewers doubted the effect of systemically-delivered antibiotics in combination with non-surgical or surgical treatment (Baus-Domínguez et al., 2023; Boccia et al., 2023), especially in the long term (Teughels et al., 2023). Besides, the side effects of systemic antibiotics can also make peri-implantitis more challenging to control. A systematic review by Verdugo et al. (2016) expressed concerns regarding the possibility of recurrent peri-implant opportunistic bacterial, viral, and yeast infections in immunocompetent patients, in which several researches advocated drug sensitivity testing prior to systemic antibiotic use, although this was not performed in these studies.

The advantages of local antibiotic administration encompass the option to attain high concentrations at the targeted site, coupled with a lower risk of adverse effects and antibiotic resistance. Similarly, repeated and regular dosing is more conducive to antibiotic efficacy, and the patient's compliance does not affect the clinical advantages. The major drawbacks include significant cost and the need for experienced dentists to administer the treatment. The meta-analysis indicated substantial improvements in PPD (WMD=0.67, 95% CI 0.24 to 1.10), I^2=0%, SR (WMD=2.32, 95% CI 1.06 to 5.06, I^2=0%), and BL (WMD=0.78, 95% CI −0.10 to 1.66, I^2=75%) in the local antibiotic group. These findings align with the comprehensive review and meta-analysis conducted by Rovai et al. (2016), examining the supplementary impact of local antibiotic therapy in treating peri-implantitis. Furthermore, a recent analysis confirmed the promising performance of local antibiotics in surgical interventions (Baus-Domínguez et al., 2023). However, due to a paucity of data, it was difficult to interpret the results in terms of CAL and BL. What is more, Emanuel et al. (2020) found significantly higher bone growth in antibiotic groups than in control groups after 6 months (−1.08±1.25 vs. 0.24±1.14, P=0.005) and 12 months follow-up (−0.88±1.23 vs. −0.33±1.00, P=0.006), and significantly higher CAL in the antibiotic group after 12 months of follow-up (−2.21±1.27 vs. −0.42±1.38, P=0.001), suggesting that local antibiotics may also have a beneficial effect on the BL and CAL. In addition, the observation time of relevant studies on topical antibiotics was shorter, and longer observation time is required, which is consistent with Passarelli et al. (2021).

4.2 Surgical and non-surgical treatments

The adjunctive use of antibiotics in surgical treatment significantly improved PPD (WMD=0.98, 95% CI 0.35 to 1.60, I^2=37%), SR (WMD=3.24, 95% CI 1.62 to 6.48, I^2=0%), and BL (WMD=0.92, 95% CI 0.28 to 1.56, I^2=81%). Except for BL, the heterogeneities for those values were modest, making the results more plausible. However, due to the lack of CAL data, meta-analysis could not be performed. Another meta-analysis of adjuvant antibiotics in non-surgical treatment found similar results for PPD and concluded that adjuvant antibiotics can be used when mechanical debridement does not reach the therapeutic objectives (Grusovin et al., 2022). On the other hand, following a network meta-analysis investigating the impact of non-augmentative techniques in surgical interventions for peri-implantitis treatment, the adjuvant uses of systemic antibiotics did not improve additional PPD or BL in peri-implantitis treatments. This included studies that did not directly compare antibiotics with other forms of adjuvant treatment, which may explain the disparity in the conclusions.

Notably, remarkable enhancements in PPD (WMD=1.15, 95% CI 0.73 to 1.57, I^2=58%), SR (WMD=1.93, 95% CI 1.10 to 3.37, I^2=6%), and CAL (WMD=1.34, 95% CI 1.05 to 1.62, I^2=0%) were observed in the meta-analysis of adjuvant antibiotics in non-surgical treatment. The current findings are partially consistent with prior researches, which indicated that supplemental antibiotics in non-surgical treatment for peri-implantitis improved PPD and SR (Grusovin et al., 2022). There was no significant difference in BL (WMD=0.62, 95% CI −0.49 to 1.74, I^2=97%), and given the substantial overlap of data within the meta-analysis between the non-surgical treatment and systemic antibiotic subgroups, attributing the observed effect specifically to the adjunctive use of antibiotics in non-surgical therapy remains challenging. It merits attention that, within a prospective case series analysis employing systemic antibiotics, the authors posited that the efficacy of non-surgical treatment modalities is questionable (Vilarrasa et al., 2023), which inspires us to conduct further investigation.

4.3 Treatment methods used in the control groups

In this review, the control groups in two trials (Emanuel et al., 2020; Park et al., 2021) received no extra therapy, while they received placebo in other three studies (Cha et al., 2019; Shibli et al., 2019; Blanco et al., 2022). In the remaining two articles (Carcuac et al., 2016; Polymeri et al., 2022), patients in control groups were rinsed with chlorhexidine, which was applied in the antibiotic group in the study of Carcuac et al. (2016). In a way, these "control groups" did not use the updated techniques, such as laser therapy and photodynamic therapy, even if the calculations showed that the effect of adjuvant use of antibiotics was superior to other adjuvant approaches. Thus, we cannot conclude that "adjunctive antibiotics are still the best adjuvant therapy for the treatment of peri-implantitis." Rather, the utilization of adjunctive antibiotics demonstrates enhanced effectiveness in addressing peri-implantitis when compared to adjuvant chlorhexidine rinsing or no additional therapy in terms of reducing periodontal pocket depth, controlling bone resorption and attachment loss, and improving implant SR. Additionally, in another meta-analysis (Zhao et al., 2021), our research team observed no substantial disparity in the impact of supplementary photodynamic therapy or supplemental antibiotics in the treatment of peri-implant inflammation. In fact, some other systematic reviews have found different impacts for different adjunctive measures, where antimicrobials could reduce PPD via a local or systemic method (Liñares et al., 2023). Because only RCTs were included in this review, and there are currently no relevant RCTs to validate the new technologies, we need more updated and higher-quality research on the adjuvant treatment of peri-implantitis to help clinicians make more informed decisions.

4.4 Sulcus bleeding index and microbiological results

The gingival sulcus bleeding index can detect early peri-implant mucosal inflammation (Lu et al., 2018). Due to the common occurrence of bacterial biofilms, peri-implant disease often arises, and alterations in the microbiome can be used to predict treatment effectiveness (Alves et al., 2022).

Changes in the gingival bleeding index were assessed in four articles (Cha et al., 2019; Emanuel et al., 2020; Park et al., 2021; Polymeri et al., 2022), and only two of these trials revealed significant differences between the control and antibiotic groups (Emanuel et al., 2020; Park et al., 2021). Due to the diverse display techniques of bleeding on probing (BOP) scores, such as dichotomous and continuous approaches, no further data processing was performed in this work. In the previous meta-analysis review by Zhao et al. (2021), no distinction was observed between the control and antibiotic groups regarding the impact of adjunctive antimicrobial photodynamic therapy and antibiotics implemented in the treatment of peri-implantitis, which can be regarded as a reference for the effect of adjunctive antibiotics on the BOP indicator.

Microbiome results were also highlighted in five researches (Carcuac et al., 2016; Cha et al., 2019; Shibli et al., 2019; Park et al., 2021; Blanco et al., 2022), all of which discovered a substantial drop in oral microbiome following therapy. Two papers indicated microbiome regeneration after three months (Carcuac et al., 2016; Shibli et al., 2019), and the microbiota in the antibiotic groups exhibited a significant decrease throughout the entire study period. The abundance of *Porphyromonas gingivalis* in the control group at the follow-up exhibited a significant reduction compared to the initial levels (Park et al., 2021). In other studies that did not report the number rebound, groups without antibiotic treatment exhibited a substantial decrease in bacterial count. This implies that only surgical/non-surgical treatment may be "sufficient" in microflora control. Certainly, the employment of contemporary methodologies, such as the sequencing analysis technologies, is imperative to facilitate further research (Chen et al., 2023).

The varying conclusions across studies could be attributed to variations in the sampling methods used for microbiological analysis. For example, one study utilized DNA-DNA checker hybridization, but the majority of the listed studies employed colony forming unit (CFU) to determine the number of bacteria.

4.5 Strengths and limitations

The key weaknesses of this review are the inclusion of papers with a high-quality bias and the absence of pertinent RCTs. It is important to highlight that different trials may have variations in treatment techniques, materials, prosthesis management, and dosage administration, which can potentially introduce bias in the results. Furthermore, the previously mentioned treatment limitations in the control groups also contribute to potential bias. In the study by Cha et al. (2019), all patients took systemic antibiotics after therapy, which could have skewed the results. To minimize the impacts of different data selection methods and observation time on the results, we selected the average value of multiple site data at the implant level as the analysis data, and considered data recorded as much as possible beyond the follow-up period of six months. Moreover, only data from two investigations (Emanuel et al., 2020; Blanco et al., 2022) were evaluated with numerous indicators, which also reduced the representativeness of data. Finally, due to the lack of pertinent reports, it is challenging to interpret the findings of these studies regarding the harmful effects of antibiotics.

5 Conclusions

The administration of adjunctive antibiotics in the management of peri-implantitis can achieve a beneficial impact on short-term treatment outcomes, whereas possible side effects, such as drug resistance, still need to be considered. There is a lack of research comparing antibiotics to other emerging adjunctive technologies for peri-implantitis management, highlighting the need for further investigations. In general, the adjunctive use of antibiotics in the treatment of peri-implantitis still needs to be undertaken with caution.

Acknowledgments

This work was supported by the Fundamental Research Funds for the Central Universities (No. 2023QZJH59/226-2023-00155), the National Natural Science Foundation of China (Nos. 82370990 and 82201051), the Medical Health Science and Technology Project of Zhejiang Provincial Health Commission (No. WKJ-ZJ-2335), the Innovative Talent of Zhejiang Provincial Health Commission, the Zhejiang "Xinmiao" Talents Program (No. 2023R401211), China. The authors extend their sincere appreciations to Professor Angeliki POLYMERI (Academic Centre for Dentistry Amsterdam (ACTA), Department of Periodontology, University of Amsterdam, Amsterdam, the Netherlands) for kindly providing the specific number of implants in each study group and the data of change in peri-implant pocket depth and BOP (mean±SD) at implant level.

Author contributions

Yifan LU, Qianming CHEN, and Misi SI contributed to conception and design. Yifan LU, Siqi BAO, and Hongke LUO performed the data acquisition, interpretation, and statistical analysis. Yifan LU writed the first draft of the manuscript, and all authors critically reviewed the manuscript. All authors have read and approved the final manuscript, and therefore, have full access to all the data in the study and take responsibility for the integrity and security of the data.

Compliance with ethics guidelines

Qianming CHEN is an Editorial Board Member for *Journal of Zhejiang University-SCIENCE B (Biomedicine & Biotechnology)*, and was not involved in the editorial review or the decision to publish this article. Yifan LU, Siqi BAO, Hongke LUO, Qianming CHEN, and Misi SI declare that they have no conflict of interest.

This article does not contain any studies with human or animal subjects performed by any of the authors. This article followed the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and was registered with Prospective Register of Systematic Reviews (PROSPERO) (Reference No. CRD42023391623).

References

Alves CH, Russi KL, Rocha NC, et al., 2022. Host-microbiome interactions regarding peri-implantitis and dental implant loss. *J Transl Med*, 20:425.
https://doi.org/10.1186/s12967-022-03636-9

Baus-Domínguez M, Bakkali S, Hermida-Cabrera P, et al., 2023. A systematic review and meta-analysis of systemic and local antibiotic therapy in the surgical treatment of peri-implantitis. *Antibiotics*, 12(7):1223.
https://doi.org/10.3390/antibiotics12071223

Berglundh T, Armitage G, Araujo MG, et al., 2018. Peri-implant diseases and conditions: consensus report of workgroup 4 of the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions. *J Clin Periodontol*, 45(S20):S286-S291.
https://doi.org/10.1111/jcpe.12957

Blanco C, Pico A, Dopico J, et al., 2022. Adjunctive benefits of systemic metronidazole on non-surgical treatment of peri-implantitis. A randomized placebo-controlled clinical trial. *J Clin Periodontol*, 49(1):15-27.
https://doi.org/10.1111/jcpe.13564

Boccia G, di Spirito F, D'Ambrosio F, et al., 2023. Local and systemic antibiotics in peri-implantitis management: an umbrella review. *Antibiotics*, 12(1):114.
https://doi.org/10.3390/antibiotics12010114

Carcuac O, Derks J, Charalampakis G, et al., 2016. Adjunctive systemic and local antimicrobial therapy in the surgical treatment of peri-implantitis: a randomized controlled clinical trial. *J Dent Res*, 95(1):50-57.
https://doi.org/10.1177/0022034515601961

Carcuac O, Derks J, Abrahamsson I, et al., 2017. Surgical treatment of peri-implantitis: 3-year results from a randomized controlled clinical trial. *J Clin Periodontol*, 44(12): 1294-1303.
https://doi.org/10.1111/jcpe.12813

Cha JK, Lee JS, Kim CS, 2019. Surgical therapy of peri-implantitis with local minocycline: a 6-month randomized controlled clinical trial. *J Dent Res*, 98(3):288-295.
https://doi.org/10.1177/0022034518818479

Chan HL, Lin GH, Suarez F, et al., 2014. Surgical management of peri-implantitis: a systematic review and meta-analysis of treatment outcomes. *J Periodontol*, 85(8):1027-1041.
https://doi.org/10.1902/jop.2013.130563

Chen QM, Wang YH, Shuai J, 2023. Current status and future prospects of stomatology research. *J Zhejiang Univ-Sci B (Biomed & Biotechnol)*, 24(10):853-867.
https://doi.org/10.1631/jzus.B2200702

Claffey N, Clarke E, Polyzois I, et al., 2008. Surgical treatment of peri-implantitis. *J Clin Periodontol*, 35(s8):316-332.
https://doi.org/10.1111/j.1600-051X.2008.01277.x

Darby I, 2022. Risk factors for periodontitis & peri-implantitis. *Periodontol 2000*, 90(1):9-12.
https://doi.org/10.1111/prd.12447

Derks J, Tomasi C, 2015. Peri-implant health and disease. A systematic review of current epidemiology. *J Clin Periodontol*, 42(S16):S158-S171.
https://doi.org/10.1111/jcpe.12334

Emanuel N, Machtei EE, Reichart M, et al., 2020. D-PLEX$_{500}$: a local biodegradable prolonged release doxycycline-formulated bone graft for the treatment for peri-implantitis. A randomized controlled clinical study. *Quintessence Int*, 51(7):546-553.
https://doi.org/10.3290/j.qi.a44629

Feres M, Martins R, Souza JGS, et al., 2023. Unraveling the effectiveness of antibiotics for peri-implantitis treatment: a scoping review. *Clin Implant Dent Relat Res*, 25(4): 767-781.
https://doi.org/10.1111/cid.13239

Figuero E, Graziani F, Sanz I, et al., 2014. Management of peri-implant mucositis and peri-implantitis. *Periodontol 2000*, 66(1):255-273.
https://doi.org/10.1111/prd.12049

Graziani F, Karapetsa D, Alonso B, et al., 2017. Nonsurgical and surgical treatment of periodontitis: how many options for one disease? *Periodontol 2000*, 75(1):152-188.
https://doi.org/10.1111/prd.12201

Grusovin MG, Pispero A, del Fabbro M, et al., 2022. Antibiotics as adjunctive therapy in the non-surgical treatment of peri-implantitis: a systematic review and meta-analysis. *Antibiotics*, 11(12):1766.
https://doi.org/10.3390/antibiotics11121766

Heitz-Mayfield LJ, Aaboe M, Araujo M, et al., 2018. Group 4 ITI consensus report: risks and biologic complications associated with implant dentistry. *Clin Oral Implants Res*, 29(S16):351-358.
https://doi.org/10.1111/clr.13307

Heitz-Mayfield LJA, Mombelli A, 2014. The therapy of peri-implantitis: a systematic review. *Int J Oral Maxillofac Implants*, 29(Suppl):325-345.
https://doi.org/10.11607/jomi.2014suppl.g5.3

Higgins JPT, Thompson SG, Deeks JJ, et al., 2003. Measuring inconsistency in meta-analyses. *BMJ*, 327(7414):557-560.
https://doi.org/10.1136/bmj.327.7414.557

Higgins JPT, Altman DG, Gøtzsche PC, et al., 2011. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ*, 343:d5928.
https://doi.org/10.1136/bmj.d5928

Keestra JAJ, Grosjean I, Coucke W, et al., 2015. Non-surgical periodontal therapy with systemic antibiotics in patients with untreated chronic periodontitis: a systematic review and meta-analysis. *J Periodontal Res*, 50(3):294-314.
https://doi.org/10.1111/jre.12221

Khoshkam V, Chan HL, Lin GH, et al., 2013. Reconstructive procedures for treating peri-implantitis: a systematic review. *J Dent Res*, 92(12 Suppl):131S-138S.
https://doi.org/10.1177/0022034513509279

Klinge B, Gustafsson A, Berglundh T, 2002. A systematic review of the effect of anti-infective therapy in the treatment of peri-implantitis. *J Clin Periodontol*, 29(s3):213-225.
https://doi.org/10.1034/j.1600-051x.29.s3.13.x

Lee CT, Huang YW, Zhu L, et al., 2017. Prevalences of peri-implantitis and peri-implant mucositis: systematic review and meta-analysis. *J Dent*, 62:1-12.
https://doi.org/10.1016/j.jdent.2017.04.011

Li ZB, Li K, Ding T, et al., 2022. The effect of nonaugmentative approaches in the surgical treatment of peri-implantitis: a systematic review and network meta-analysis. *Int J Oral Maxillofac Implants*, 37(2):270-282.
https://doi.org/10.11607/jomi.9211

Liñares A, Sanz-Sánchez I, Dopico J, et al., 2023. Efficacy of adjunctive measures in the non-surgical treatment of peri-implantitis: a systematic review. *J Clin Periodontol*, 50(S26):224-243.
https://doi.org/10.1111/jcpe.13821

Lu HL, Tang HF, Zhou T, et al., 2018. Assessment of the periodontal health status in patients undergoing orthodontic treatment with fixed appliances and Invisalign system: a meta-analysis. *Medicine*, 97(13):e0248.
https://doi.org/10.1097/MD.0000000000010248

Mombelli A, Lang NP, 1992. Antimicrobial treatment of peri-implant infections. *Clin Oral Implants Res*, 3(4):162-168.
https://doi.org/10.1034/j.1600-0501.1992.030402.x

Park SH, Song YW, Cha JK, et al., 2021. Adjunctive use of metronidazole-minocycline ointment in the nonsurgical treatment of peri-implantitis: a multicenter randomized controlled trial. *Clin Implant Dent Relat Res*, 23(4):543-554.
https://doi.org/10.1111/cid.13006

Passarelli PC, Netti A, Lopez MA, et al., 2021. Local/topical antibiotics for peri-implantitis treatment: a systematic review. *Antibiotics*, 10(11):1298.
https://doi.org/10.3390/antibiotics10111298

Polymeri A, van der Horst J, Anssari Moin D, et al., 2022. Non-surgical peri-implantitis treatment with or without systemic antibiotics: a randomized controlled clinical trial. *Clin Oral Implants Res*, 33(5):548-557.
https://doi.org/10.1111/clr.13914

Renvert S, Roos-Jansåker AM, Lindahl C, et al., 2007. Infection at titanium implants with or without a clinical diagnosis of inflammation. *Clin Oral Implants Res*, 18(4): 509-516.
https://doi.org/10.1111/j.1600-0501.2007.01378.x

Rovai ES, Souto MLS, Ganhito JA, et al., 2016. Efficacy of local antimicrobials in the non-surgical treatment of patients with periodontitis and diabetes: a systematic review. *J Periodontol*, 87(12):1406-1417.
https://doi.org/10.1902/jop.2016.160214

Santos RS, Macedo RF, Souza EA, et al., 2016. The use of systemic antibiotics in the treatment of refractory periodontitis: a systematic review. *J Am Dent Assoc*, 147(7): 577-585.
https://doi.org/10.1016/j.adaj.2016.02.013

Shibli JA, Ferrari DS, Siroma RS, et al., 2019. Microbiological and clinical effects of adjunctive systemic metronidazole and amoxicillin in the non-surgical treatment of peri-implantitis: 1 year follow-up. *Braz Oral Res*, 33(S1): e080.
https://doi.org/10.1590/1807-3107bor-2019.vol33.0080

Singh R, Sripada L, Singh R, 2014. Side effects of antibiotics during bacterial infection: mitochondria, the main target in host cell. *Mitochondrion*, 16:50-54.

https://doi.org/10.1016/j.mito.2013.10.005

Smeets R, Henningsen A, Jung O, et al., 2014. Definition, etiology, prevention and treatment of peri-implantitis – a review. *Head Face Med*, 10:34.
https://doi.org/10.1186/1746-160X-10-34

Teughels W, Seyssens L, Christiaens V, et al., 2023. Adjunctive locally and systemically delivered antimicrobials during surgical treatment of peri-implantitis: a systematic review. *J Clin Periodontol*, 50(S26):359-372.
https://doi.org/10.1111/jcpe.13773

Verdugo F, Laksmana T, Uribarri A, 2016. Systemic antibiotics and the risk of superinfection in peri-implantitis. *Arch Oral Biol*, 64:39-50.
https://doi.org/10.1016/j.archoralbio.2015.12.007

Vilarrasa J, Soldini MC, Pons R, et al., 2023. Outcome indicators of non-surgical therapy of peri-implantitis: a prospective case series analysis. *Clin Oral Investig*, 27(6): 3125-3138.
https://doi.org/10.1007/s00784-023-04918-2

Wang Y, Chen CY, Stathopoulou PG, et al., 2022. Efficacy of antibiotics used as an adjunct in the treatment of peri-implant mucositis and peri-implantitis: a systematic review and meta-analysis. *Int J Oral Maxillofac Implants*, 37(2): 235-249.
https://doi.org/10.11607/jomi.9220

Yong JW, Gröger S, von Bremen J, et al., 2023. Photobiomodulation therapy assisted orthodontic tooth movement: potential implications, challenges, and new perspectives. *J Zhejiang Univ-Sci B (Biomed & Biotechnol)*, 24(11):957-973.
https://doi.org/10.1631/jzus.B2200706

Zhang HD, Li WJ, Zhang L, et al., 2018. A nomogram prediction of peri-implantitis in treated severe periodontitis patients: a 1–5-year prospective cohort study. *Clin Implant Dent Relat Res*, 20(6):962-968.
https://doi.org/10.1111/cid.12686

Zhao XT, Lin HB, Ding T, et al., 2023. Overview of the main biological mechanisms linked to changes in periodontal ligament stem cells and the inflammatory microenvironment. *J Zhejiang Univ-Sci B (Biomed & Biotechnol)*, 24(5): 373-386.
https://doi.org/10.1631/jzus.B2200576

Zhao YX, Pu R, Qian YJ, et al., 2021. Antimicrobial photodynamic therapy versus antibiotics as an adjunct in the treatment of periodontitis and peri-implantitis: a systematic review and meta-analysis. *Photodiagnosis Photodyn Ther*, 34:102231.
https://doi.org/10.1016/j.pdpdt.2021.102231

Zitzmann NU, Berglundh T, Marinello CP, et al., 2001. Experimental peri-implant mucositis in man. *J Clin Periodontol*, 28(6):517-523.
https://doi.org/10.1034/j.1600-051x.2001.028006517.x

Supplementary information

Tables S1–S3